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Original article

Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles

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ABSTRACT

A new class of amido linked bis heterocycles *viz*., pyrrolyl/pyrazolyl-oxazoles, thiazoles and imidazoles were prepared by 1,3-dipolar cycloaddition of TosMIC and diazomethane to the respective cinnamamide derivatives and screened for antimicrobial activity. The chlorosubstituted imidazolyl cinnamamide (6c) is the most potential antimicrobial agent as it displayed strong antibacterial activity against *Bacillus subtilis* and antifungal activity against *Penicillium chrysogenum*.

1. Introduction

Azoles constitute immensely important members of the aromatic heterocycle family due to their presence in a myriad of bioactive natural products as privileged pharmacophores. The pyrrole motif attracts particular attention in methodology design for its utility as a synthetic building block and widespread occurrence in target structures, such as functional materials and biologically-relevant compounds [1–5]. Among the highly marketed COX-2 inhibitors that comprise the pyrazole nucleus, celecoxib is the one which is treated as a safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocyclic template that is known to selectively inhibit the COX-2 enzyme. Some other examples of pyrazole derivatives as NSAIDs are mefobutazone, ramifenazone, famprofazone [6–9]. The oxazole ring is endowed with various activities such as hypoglycemic [10], analgesic [11], anti-inflammatory [12] and antibacterial. Besides, oxazoles showed antiproliferative activity against many cancer cells, especially human prostate cancer and human epidermoid carcinoma [13–15]. The thiazolyl group is also of great importance as it appears frequently in the structures of various natural products and biologically active compounds like thiamine (vitamin-B) and also in some antibiotic drugs like penicillin, micrococcin [16] and many metabolic products of fungi and primitive marine animals etc. In recent years, the high therapeutic properties of the imidazole related drugs have been attracting the attention of medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Medicinal properties of imidazole containing compounds include anticancer [17], antimicrobial [18–21] and antioxidant [22]. It is known that clinically useful drugs such as miconazole, econazole and oxiconazole having imidazole moiety exhibit strong antifungal activity. In fact, polyamides composed of *N*-methylpyrrole, *N*-methylimidazole and large varieties of analogous five membered heteroaromatic amino acids have been designed with predictable sequence selectivity and many of these designed polyamides bind in the DNA minor groove with high affinities [23–25]. Motivated by the aforesaid findings and pursing our studies on different five membered heterocycles [26], we were designed to synthesize a new series of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles and tested them as antimicrobial agents.

2. Chemistry

The synthetic pathway that leads to the formation of the title compounds **7**-**15** are sketched in Scheme 1. By adopting the literature precedent 4-aryloxazol-2-amine (**1**), 4-arylthiazol-2-amine (**2**) and 4-aryl-1*H*-imidazol-2-amine (**3**) were prepared from the

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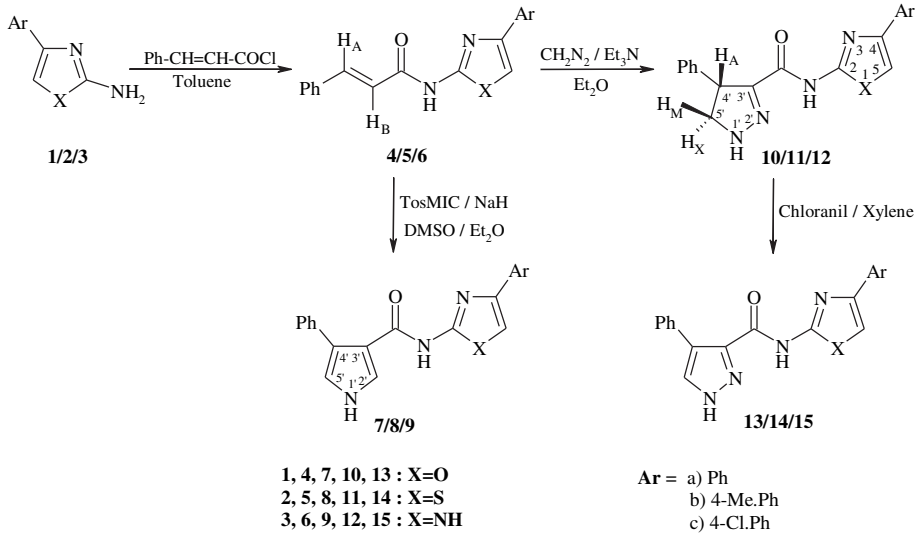

Scheme 1. Pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles.

synthetic intermediate, phenacyl bromide [27,28]. Aromatic heterocyclic styrylamides, (*E*)-*N*-(4-aryloxazol-2-yl)cinnamamide (**4**), (*E*)-*N*-(4-arylthiazol-2-yl)cinnamamide (**5**) and (*E*)-*N*-(4-aryl-1*H*-imidazol-2-yl)cinnamamide (**6**) were prepared by the reaction of **1**, **2** and **3** with cinnamoyl chloride (Scheme 1). The ^{1}H NMR spectra of **4a**, **5a** and **6a** showed a singlet at δ 7.60, 7.50 and 7.52 due to C_5—H and another broad singlet at 8.35, 8.28 and 8.21 ppm due to NH. The **6a** also showed a broad singlet at 11.20 due to NH of imidazole ring. The signals of NH disappeared on deuteration. In addition, two doublets were observed at δ 7.88, 7.81, 7.75 and 6.71, 6.43, 6.39 ppm which were assigned to olefin protons, H_A and H_B, respectively. The coupling constant value J_{AB} ~16.0 Hz indicated that they are in *trans* geometry. The olefin moiety present in these compounds was used to develop pyrrole [29] and pyrazole [30] units. Thus treatment of **4**, **5** and **6** with tosylmethyl isocyanide in the presence of sodium hydride in a mixture of dimethyl sulfoxide and ether produced 4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**7**), 4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**8**) and 4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**9**) (Scheme 1). The ^{1}H NMR spectra of **7a** displayed three singlets at δ 7.65, 6.82 7.10, **8a** at 7.74, 6.62, 6.68 and **9a** at 7.77, 6.58, 6.81 ppm due to C_5—H, $C_{2'}$—H and $C_{5'}$—H, respectively. Furthermore, two broad singlets were observed at δ 9.87, 9.81, 9.85 due to NH of pyrrole ring and at 8.23, 8.12, 8.25 due to CONH in these compounds. In addition, compound **9a** displayed a broad singlet at 11.46 due to NH of imidazole ring. Apart from these, the olefin moiety present in **4**, **5** and **6** was used to develop pyrazoline ring by 1,3-dipolar cycloaddition of diazomethane in ether in the presence of triethylamine at −20° to −15 °C for 42—48 h. The compounds 4′,5′-dihydro-4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**10**), 4′,5′-dihydro-4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**11**) and 4′,5′-dihydro-4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**12**) obtained were characterized by spectral parameters (Scheme 1). In the ^{1}H NMR spectra of **10a**, **11a** and **12a**, the methine and methylene protons of pyrazoline ring displayed an AMX splitting pattern. The three double doublets observed at δ 4.43, 4.02, 3.60 in **10a**, at 4.38, 4.21, 3.58 in **11a** and at 4.40, 4.11, 3.66 ppm in **12a** were assigned to H_A, H_M and H_X. The coupling constant values J_{AM} = 11.6, J_{AX} = 6.1, J_{MX} = 11.1 in **10a**, J_{AM} = 11.7, J_{AX} = 6.2, J_{MX} = 11.2 in **11a** and J_{AM} = 11.5, J_{AX} = 6.4, J_{MX} = 11.3 Hz in **12a** indicated that H_A, H_M are *cis*, H_A, H_X are *trans* while H_M, H_X are *geminal*. Apart from these, the C_5—H displayed a singlet at δ 7.65 in **10a**, at 7.72 in **11a** and at 7.68 ppm in **12a**. However, two broad singlets were observed at 8.98, 8.41 in **10a**, 8.81, 8.48 in **11a**, and 8.13, 8.02 in **12a** due to NH of pyrazoline and CONH, respectively which disappeared on deuteration. Aromatization of pyrazoline ring in **10**, **11** and **12** was effected by treating the latter compounds with chloranil in xylene to produce 4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**13**), 4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**14**) and 4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**15**). The ^{1}H NMR spectra of **13a** displayed two singlets at δ 7.60, 6.24, **14a** at 7.30, 6.31 and **15a** at 7.58, 6.12 ppm which were assigned for C_5—H and $C_{5'}$—H. Moreover, a broad singlet was observed at δ 6.61, 6.40 and 6.52 ppm in these compounds due to pyrazolyl NH which disappeared on deuteration. The structures of all the compounds were further ascertained by IR and ^{13}C NMR spectral data.

3. Antimicrobial activity

The results of antibacterial activity shown in Table 1 indicated that Gram-negative bacteria were more susceptible towards the tested compounds than Gram positive ones. When compared to the standard drug Chloramphenicol it was seen that **6c** and **15c** were effective particularly against *Pseudomonas aeruginosa* at 100 μg/ml. Amongst bis heterocyclic compounds, the aromatized bis heterocycles **13**, **14** and **15** were effective than the corresponding non-aromatized compounds **10**, **11** and **12**. Amongst pyrrole and pyrazole containing bis heterocycles, the latter compounds **13**, **14** and **15** displayed greater activity. The presence of chloro substituent on the aromatic ring enhances the activity (Fig. 1).

All the tested compounds inhibited the spore germination against tested fungi except the compound **10**. In general, most of the compounds showed slightly higher antifungal activity towards *Penicillium chrysogenum* than *Aspergillus niger*. The compounds **6c** and **15c** displayed excellent activity particularly against *P. chrysogenum* almost equivalent to the standard drug Ketoconazole (Table 2 and Fig. 2).

The MIC, MBC and MFC values of the compounds tested are listed in Table 3. The compound **6c** exhibited low MIC values when compared with **9c** and **15c**. In addition MBC value is 2×MIC in case of *Bacillus subtilis* and MFC value is 2×MIC in case of *P. chrysogenum*. However the other compounds showed the bactericidal and

Table 1
The *in-vitro* antibacterial activity of compounds **4**–**15**.

Compound	Concentration (μg)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*
4a	50	12	15	–	–
	100	15	16	–	–
4b	50	–	–	–	–
	100	–	–	–	–
4c	50	22	20	21	24
	100	25	24	22	27
5a	50	21	24	17	26
	100	23	26	18	28
5b	50	20	23	15	25
	100	22	25	17	27
5c	50	29	27	25	33
	100	32	29	27	35
6a	50	19	22	16	24
	100	21	24	17	26
6b	50	18	21	14	23
	100	20	23	16	25
6c	50	32	36	31	39
	100	35	38	33	40
7a	50	12	13	–	–
	100	14	15	–	–
7b	50	–	–	–	–
	100	–	–	–	–
7c	50	18	17	18	23
	100	20	21	20	25
8a	50	17	20	15	22
	100	19	22	16	24
8b	50	16	19	13	21
	100	18	21	15	23
8c	50	26	27	23	29
	100	27	29	25	30
9a	50	15	18	14	20
	100	17	20	15	22
9b	50	14	17	13	19
	100	16	19	14	21
9c	50	30	29	25	34
	100	33	33	28	36
10a	50	–	–	–	–
	100	–	–	–	–
10b	50	–	–	–	–
	100	–	–	–	–
10c	50	17	17	17	22
	100	18	20	19	24
11a	50	13	14	–	–
	100	15	16	–	–
11b	50	13	16	12	18
	100	15	18	13	20
11c	50	24	25	22	25
	100	27	26	23	28
12a	50	12	15	12	17
	100	14	17	14	19
12b	50	11	14	11	16
	100	13	16	13	18
12c	50	25	24	21	28
	100	27	27	24	30
13a	50	10	13	10	15
	100	12	15	12	17
13b	50	–	–	–	–
	100	–	–	–	–
13c	50	20	21	19	23
	100	23	22	21	24
14a	50	9	12	9	14
	100	12	14	11	16
14b	50	9	10	8	13
	100	11	13	11	15
14c	50	27	28	24	30
	100	29	31	26	33
15a	50	8	10	9	12
	100	10	13	11	14
15b	50	8	9	9	11
	100	9	12	10	13

(*continued on next page*)

Table 1 (*continued*)

Compound	Concentration (μg)	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
		S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*
15c	50	31	33	30	37
	100	34	35	32	39
Chloramphenicol	50	33	34	27	40
	100	35	38	30	42
Control (DMSO)		–	–	–	–

(–) No activity.

fungicidal effects greater than 2×MIC. The structure–antimicrobial activity relationship of the synthesized compounds revealed that mono heterocyclic systems with extended conjugation **4**, **5**, and **6** are more active than the corresponding bis heterocyclic systems. It was also observed that the compounds having thiazole ring **5**, **8**, **14** and imidazole ring **6**, **9**, **15** were more effective when compared with compounds having oxazole unit **4**, **7**, **13**. Amongst the tested compounds, chlorosubstituted imidazolyl cinnamamide **6c** showed strong antibacterial activity against *B. subtilis* with an inhibition zone of 38 mm at 100 μg and MIC and MBC of 12.5 and 25 μg, respectively. The compound **6c** also exhibited strong antifungal activity against *P. chrysogenum* with an inhibition zone of 38 mm at 100 μg and MIC and MFC of 25 and 50 μg, respectively.

4. Conclusion

A new class of amido linked bis heterocycles *viz*., pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles were prepared from 4-aryloxazol-2-amine, 4-arylthiazol-2-amine and 4-aryl-1*H*-imidazol-2-amine adopting standard synthetic methodologies and tested for antimicrobial activity. Amongst bis heterocyclic systems the compounds having thiazole and imidazole units exhibited greater activity. The mono heterocyclic compounds with extended conjugation are comparatively more active than the corresponding bis heterocyclic systems.

5. Experimental section

5.1. Chemistry

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate-hexane, 0.5:2). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM λ-400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Jeol JNM spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on Perkin–Elmer 240C elemental analyzer. The compounds 4-aryloxazol-2-amine (**1**), 4-arylthiazol-2-amine (**2**) and 4-aryl-1*H*-imidazol-2-amine (**3**) were prepared as per the literature procedure [27,28].

5.1.1. General procedure for the synthesis of (E)-N-(4-aryloxazol-2-yl)cinnamamide (**4a**–**c**)/(E)-N-(4-arylthiazol-2-yl)cinnamamide-(**5a**–**c**)/(E)-N-(4-aryl-1H-imidazol-2-yl)cinnamamide (**6a**–**c**)

The compound 4-phenyloxazol-2-amine (**1**)/4-phenylthiazol-2-amine (**2**)/4-phenyl-1*H*-imidazol-2-amine (**3**) (1 mmol), cinnamoyl chloride (0.18 g, 1.1 mmol) and toluene were heated to reflux for 15–18 h. The reaction mixture was cooled and the product was

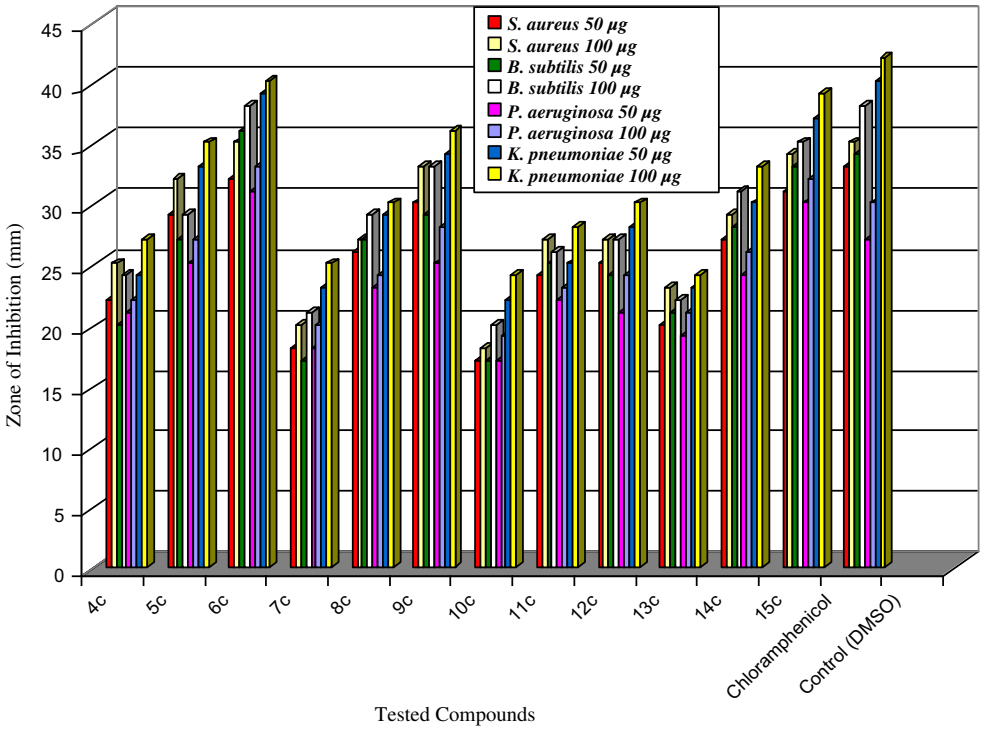

Fig. 1. Antibacterial activity of **4c**–**15c**.

Table 2
The *in-vitro* antifungal activity of compounds **4**–**15**.

Compound	Concentration (μg)	Zone of inhibition (mm)	
		A. niger	*P. chrysogenum*
4a	50	–	–
	100	–	–
4b	50	–	–
	100	–	–
4c	50	25	27
	100	28	30
5a	50	21	23
	100	24	26
5b	50	19	22
	100	23	25
5c	50	31	32
	100	33	35
6a	50	19	21
	100	22	24
6b	50	18	20
	100	21	23
6c	50	32	35
	100	34	38
7a	50	–	–
	100	–	–
7b	50	–	–
	100	–	–
7c	50	24	25
	100	26	28
8a	50	18	19
	100	20	22
8b	50	18	18
	100	19	21
8c	50	29	30
	100	31	33
9a	50	16	17
	100	18	20
9b	50	14	16
	100	17	19
9c	50	32	33
	100	34	36
10a	50	–	–
	100	–	–
10b	50	–	–
	100	–	–
10c	50	23	24
	100	25	27
11a	50	–	–
	100	–	–
11b	50	13	15
	100	16	18
11c	50	28	28
	100	29	31
12a	50	13	14
	100	15	17
12b	50	11	13
	100	14	16
12c	50	28	29
	100	30	32
13a	50	10	12
	100	13	15
13b	50	–	–
	100	–	–
13c	50	24	26
	100	27	29
14a	50	9	11
	100	12	14
14b	50	8	10
	100	11	13
14c	50	30	31
	100	32	34
15a	50	8	9
	100	10	12
15b	50	8	8
	100	9	11
15c	50	30	33
	100	34	37
Ketoconazole	50	33	36
	100	36	38
Control (DMSO)		–	–

(–) No activity.

decolourised by treating it with 50/50 carbon/celite (v/v). The reaction mixture was poured through a pad of silica gel (50 ml) and eluted the product with 10% ethyl acetate/hexane. The crude product was then recrystallized from ethyl acetate/hexane.

*5.1.1.1. (E)-N-(4-Phenyloxazol-2-yl)cinnamamide (**4a**).* Yellow solid (0.24 g, 85%); m.p. 145–147 °C; IR (KBr): 3320 (NH), 1628 (*C*ONH), 1625 (C=C), 1574 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.71 (d, 1H, H_B, J = 16.0 Hz), 7.24–7.65 (m, 11H, Ar–H and C_5–H), 7.88 (d, 1H, H_A, J = 16.0 Hz), 8.35 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 118.2 (C–H_B), 136.5 (C_5), 138.2 (C_4), 148.2 (C–H_A), 158.2 (C_2), 166.5 (C=O), 126.2, 127.1, 128.5, 129.8, 133.0, 135.1 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.46; H, 4.86; N, 9.64; Found: C, 74.52; H, 4.87; N, 9.72%.

*5.1.1.2. (E)-N-(4-p-Tolyloxazol-2-yl)cinnamamide (**4b**).* Yellow solid (0.24 g, 80%); m.p. 130–132 °C; IR (KBr): 3315 (NH), 1658 (*C*ONH), 1620 (C=C), 1568 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H, Ar–CH_3), 6.69 (d, 1H, H_B, J = 16.2 Hz), 7.21–7.52 (m, 10H, Ar–H and C_5–H), 7.79 (d, 1H, H_A, J = 16.2 Hz), 8.31 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 24.3 (Ar–CH_3), 118.0 (C–H_B), 137.1 (C_5), 139.5 (C_4), 147.6 (C–H_A), 157.7 (C_2), 166.1 (C=O), 126.0, 127.4, 127.9, 128.4, 129.5, 130.6, 135.0, 138.2 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.29; N, 9.20; Found: C, 75.07; H, 5.28; N, 9.27%.

*5.1.1.3. (E)-N-(4-(p-Chlorophenyl)oxazol-2-yl)cinnamamide (**4c**).* Yellow solid (0.28 g, 88%); m.p. 154–156 °C; IR (KBr): 3327 (NH), 1630 (*C*ONH), 1628 (C=C), 1575 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (d, 1H, H_B, J = 16.1 Hz), 7.18–7.36 (m, 10H, Ar–H and C_5–H), 7.89 (d, 1H, H_A, J = 16.1 Hz), 8.40 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 118.8 (C–H_B), 137.8 (C_5), 141.0 (C_4), 148.9 (C–H_A), 158.5 (C_2), 166.9 (C=O), 126.3, 127.6, 128.2, 129.1, 129.8, 131.3, 134.1135.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.62; Found: C, 66.52; H, 4.02; N, 8.68%.

*5.1.1.4. (E)-N-(4-Phenylthiazol-2-yl)cinnamamide (**5a**).* Yellow solid (0.26 g, 85%); m.p. 148–150 °C; IR (KBr): 3324 (NH), 1645 (*C*ONH), 1630 (C=C), 1562 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.43 (d, 1H, H_B, J = 15.8 Hz), 7.21–7.55 (m, 11H, Ar–H and C_5–H), 7.81 (d, 1H, H_A, J = 15.8 Hz), 8.28 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 116.4 (C_5), 117.1 (C–H_B), 146.8 (C–H_A), 148.5 (C_4), 162.3 (C_2), 170.0 (C=O), 126.1, 127.2, 128.0, 128.5, 128.8, 129.3, 133.2, 135.2 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14; Found: C, 70.63; H, 4.63; N, 9.20%.

*5.1.1.5. (E)-N-(4-p-Tolylthiazol-2-yl)cinnamamide (**5b**).* Yellow solid (0.25 g, 80%); m.p. 136–138 °C; IR (KBr): 3322 (NH), 1641 (*C*ONH), 1626 (C=C), 1578 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H, Ar–CH_3), 6.38 (d, 1H, H_B, J = 15.7 Hz), 7.12–7.51 (m, 10H, Ar–H and C_5–H), 7.79 (d, 1H, H_A, J = 15.7 Hz), 8.24 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 23.6 (Ar–CH_3), 116.0 (C_5), 117.0

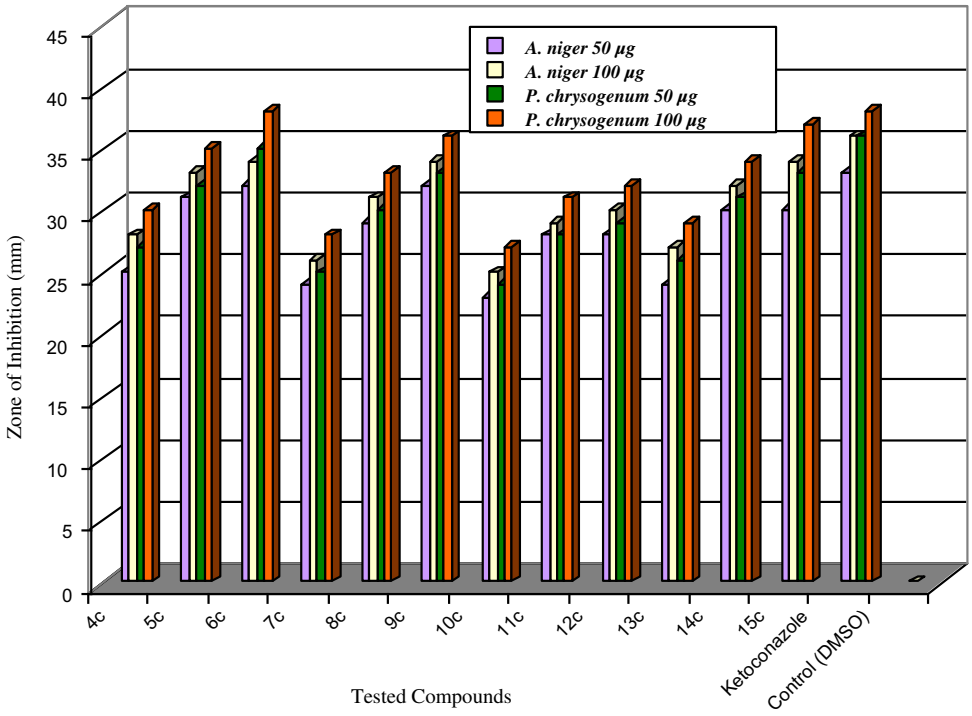

Fig. 2. Antifungal activity of **4c**–**15c**.

(C–H_B), 146.8 (C–H_A), 148.3 (C_4), 161.6 (C_2), 169.4 (C=O), 126.4, 127.1, 128.0, 128.6, 129.1, 130.0, 135.2, 138.1 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74; Found: C, 71.30; H, 5.05; N, 8.70%.

5.1.1.6. (E)-N-(4-(p-Chlorophenyl)thiazol-2-yl)cinnamamide (***5c***). Yellow solid (0.27 g, 82%); m.p. 165–167 °C; IR (KBr): 3330 (NH), 1648 (*C*ONH), 1633 (C=C), 1580 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.47 (d, 1H, H_B, J = 15.9 Hz), 7.25–7.58 (m, 10H, Ar–H and C_5–H), 7.84 (d, 1H, H_A, J = 15.9 Hz), 8.30 (bs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 116.7 (C_5), 117.3 (C–H_B), 147.0 (C–H_A), 148.7 (C_4), 162.5 (C_2), 172.3 (C=O), 126.3, 127.8, 128.0, 128.6, 129.3, 131.3, 134.0, 135.0 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{13}ClN_2OS$: C, 63.43; H, 3.84; N, 8.21; Found: C, 63.40; H, 3.87; N, 8.27%.

5.1.1.7. (E)-N-(4-Phenyl-1H-imidazol-2-yl)cinnamamide (***6a***). Yellow solid (0.22 g, 78%); m.p. 173–175 °C; IR (KBr): 3334 (NH), 1635 (*C*ONH), 1627 (C=C), 1571 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.39 (d, 1H, H_B, J = 16.1 Hz), 7.23–7.52 (m, 11H, Ar–H and C_5–H), 7.75 (d, 1H, H_A, J = 16.1 Hz), 8.21 (bs, 1H, CO–NH), 11.20 (bs, 1H, C_5–NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 119.2 (C–H_B), 121.0 (C_5), 131.2 (C_2), 142.3 (C_4), 147.3 (C–H_A), 169.0 (C=O), 126.1, 127.2, 128.6, 129.4, 133.0, 135.2 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.22; N, 14.52; Found: C, 74.78; H, 5.25; N, 14.56%.

5.1.1.8. (E)-N-(4-p-Tolyl-1H-imidazol-2-yl)cinnamamide (***6b***). Yellow solid (0.23 g, 76%); m.p. 180–182 °C; IR (KBr): 3227 (NH), 1630 (*C*ONH), 1629 (C=C), 1587 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, Ar–CH_3) 6.37 (d, 1H, H_B, J = 16.0 Hz), 7.15–7.47 (m, 10H, Ar–H and C_5–H), 7.68 (d, 1H, H_A, J = 16.0 Hz), 8.34 (bs, 1H, CO–NH), 11.16 (bs, 1H, C_5–NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 24.7 (Ar–CH_3), 119.0 (C–H_B), 120.8 (C_5), 130.9 (C_2), 142.2 (C_4), 147.1 (C–H_A), 168.4 (C=O), 125.8, 127.0, 128.1, 128.7, 129.4, 130.0, 135.0, 138.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.22; H, 5.64; N, 13.85; Found: C, 75.26; H, 5.63; N, 13.92%.

5.1.1.9. (E)-N-(4-(p-Chlorophenyl)-1H-imidazol-2-yl)cinnamamide (***6c***). Yellow solid (0.26 g, 81%); m.p. 192–194 °C; IR (KBr): 3239 (NH), 1640 (*C*ONH), 1635 (C=C), 1621 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.42 (d, 1H, H_B, J = 16.2 Hz), 7.18–7.46 (m, 10H, Ar–H and C_5–H), 7.76 (d, 1H, H_A, J = 16.2 Hz), 8.41 (bs, 1H, CO–NH), 11.24 (bs, 1H, C_5–NH) ppm; ^{13}C NMR ($CDCl_3$,100 MHz): δ 119.5 (C–H_B), 121.7 (C_5), 131.6 (C_2), 142.8 (C_4), 147.6 (C–H_A), 169.3 (C=O), 125.3, 126.8, 128.4, 129.1, 129.6, 131.1, 134.3, 135.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.35; N, 12.97; Found: C, 66.84; H, 4.38; N, 13.06%.

Table 3
MIC, MBC and MFC of compounds **6c**, **9c** and **15c**.

Compound	Minimum inhibitory concentration					
	MIC (MBC/MFC) µg					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*P. chrysogenum*
6c	12.5 (50)	12.5 (25)	12.5 (50)	25 (100)	12.5 (100)	25 (50)
9c	50 (200)	25 (100)	50 (>200)	100(>200)	25 (100)	50 (>200)
15c	50 (200)	12.5 (50)	25 (100)	50 (200)	12.5 (50)	25 (100)
Chloramphenicol	6.25	6.25	6.25	12.5	–	–
Ketoconazole	–	–	–	–	6.25	12.5

*5.1.2. General procedure for synthesis of 4-phenyl-N-(4′-aryloxazol-2-yl)-1′H-pyrrole-3′-carboxamide (**7a**–**c**)/4′-phenyl-N-(4-arylthiazol-2-yl)-1′H-pyrrole-3′-carboxamide (**8a**–**c**)/4′-phenyl-N-(4-aryl-1H-imidazol-2-yl)-1′H-pyrrole-3′-carboxamide (**9a**–**c**)*

A mixture of TosMIC (0.19 g, 1 mmol) and **4**/**5**/**6** (1 mmol) in Et_2O/DMSO (2:1) was added dropwise to a stirred mixture of NaH (0.05 g) in dry Et_2O (10 ml) at room temperature and stirring was continued for 12–14 h. Then the reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried (an. Na_2SO_4) and the solvent was removed under reduced pressure. The resultant solid was purified by passing through a column of silica gel (60–120 mesh) using ethyl acetate-hexane 1:2 as eluent.

*5.1.2.1. 4′-Phenyl-N-(4-phenyloxazol-2-yl)-1′H-pyrrole-3′-carboxamide (**7a**).* Brown solid (0.24 g, 75%); m.p. 158–160 °C; IR (KBr): 3227 (NH), 1681 (*C*ONH), 1590 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.82 (s, 1H, $C_{2'}$–H), 7.10 (s, 1H, $C_{5'}$–H), 7.21–7.68 (m, 11H, Ar–H and C_5–H), 8.23 (bs, 1H, CO–NH), 9.87 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 110.5 ($C_{3'}$), 114.6 ($C_{5'}$), 122.5 ($C_{2'}$) 127.8 ($C_{4'}$), 138.2 (C_5), 141.0 (C_4), 154.4 (C_2), 164.6 (C=O), 127.3, 128.3, 129.0, 129.8, 133.8, 136.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.93; H, 4.59; N, 12.75; Found: C, 73.03; H, 4.61; N, 12.70%.

*5.1.2.2. 4′-Phenyl-N-(4-p-tolyloxazol-2-yl)-1′H-pyrrole-3′-carboxamide (**7b**).* Brown solid (0.24 g, 72%); m.p. 145–147 °C; IR (KBr): 3221 (NH), 1674 (*C*ONH), 1572 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.34 (s, 3H, Ar–CH_3), 6.80, (s, 1H, $C_{2'}$–H), 7.00 (s, 1H, $C_{5'}$–H), 7.61–7.80 (m, 10H, Ar–H, and C_5–H), 8.21 (bs, 1H, CO–NH), 9.74 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 23.7 (Ar–CH_3), 109.8 ($C_{3'}$), 114.0 ($C_{5'}$), 122.2 ($C_{2'}$) 127.3 ($C_{4'}$), 137.8 (C_5), 139.2 (C_4), 153.0 (C_2), 163.1 (C=O), 127.4, 128.1128.9, 129.2, 130.1, 131.4, 136.2, 138.0 (aromatic carbons) ppm; Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.98; N, 12.23; Found: C, 73.53; H, 5.00; N, 12.31%.

*5.1.2.3. N-(4-(p-Chlorophenyl)oxazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**7c**).* Brown solid (0.28 g, 77%); m.p. 162–164 °C; IR (KBr): 3231 (NH), 1678 (*C*ONH), 1560 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.84 (s, 1H, $C_{2'}$–H), 7.12 (s, 1H, $C_{5'}$–H), 7.54–7.79 (m, 10H, Ar–H and C_5–H), 8.43 (bs, 1H, CO–NH), 9.89 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 111.3 ($C_{3'}$), 114.6 ($C_{5'}$), 122.9 ($C_{2'}$) 127.9 ($C_{4'}$), 138.6 (C_5), 141.4 (C_4), 153.6 (C_2), 165.3 (C=O), 127.6, 128.4, 128.8, 129.2, 129.6, 131.9, 134.3, 135.9 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{14}ClN_3O_2$: C, 66.03; H, 3.87; N, 11.55; Found: C, 66.09; H, 3.83; N, 11.62%.

*5.1.2.4. 4′-Phenyl-N-(4-phenylthiazol-2-yl)-1′H-pyrrole-3′-carboxamide (**8a**).* Brown solid (0.28 g, 83%); m.p. 178–180 °C; IR (KBr): 3238 (NH), 1661 (*C*ONH), 1577 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.62 (s, 1H, $C_{2'}$–H), 6.68 (s, 1H, $C_{5'}$–H), 7.25–7.76 (m, 11H, Ar–H and C_5–H), 8.12 (bs, 1H, CO–NH), 9.81 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 102.0 (C_5), 113.3 ($C_{3'}$), 115.5 ($C_{5'}$), 123.0 ($C_{2'}$), 128.6 ($C_{4'}$), 145.9 (C_4), 163.1 (C_2), 167.5 (C=O), 126.9, 128.6, 129.4, 130.4, 133.4, 136.0 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.37; N, 12.16; Found: C, 69.50; H, 4.39; N, 12.20%.

*5.1.2.5. 4′-Phenyl-N-(4-p-tolylthiazol-2-yl)-1′H-pyrrole-3′-carboxamide (**8b**).* Brown solid (0.30 g, 85%); m.p. 187–189 °C; IR (KBr): 3229 (NH), 1659 (*C*ONH), 1569 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3H, Ar–CH_3), 6.60 (s, 1H, $C_{2'}$–H), 6.63 (s, 1H, $C_{5'}$–H), 7.31–7.83 (m, 10H, Ar–H and C_5–H), 8.09 (bs, 1H, CO–NH), 9.76 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.8 (Ar–CH_3), 101.9 (C_5), 113.0 ($C_{3'}$), 115.2 ($C_{5'}$), 123.6 ($C_{2'}$), 128.1 ($C_{4'}$), 146.6 (C_4), 162.8 (C_2), 167.2 (C=O), 127.3, 127.8, 128.3, 129.6, 129.8, 130.3, 137.8 (aromatic carbons) ppm; Anal. Calcd. for $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.76; N, 11.69; Found: C, 70.23; H, 4.77; N, 11.75%.

*5.1.2.6. N-(4-(p-Chlorophenyl)thiazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**8c**).* Brown solid (0.33 g, 87%); m.p. 196–198 °C; IR (KBr): 3241 (NH), 1671 (*C*ONH), 1567 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.65 (s, 1H, $C_{2'}$–H), 6.71 (s, 1H, $C_{5'}$–H), 7.25–7.86 (m, 10H, Ar–H and C_5–H), 8.19 (bs, 1H, CO–NH), 9.92 (bs, 1H, $C_{2'}$–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 102.3 (C_5), 113.9 ($C_{3'}$), 115.8 ($C_{5'}$), 124.5 ($C_{2'}$), 128.8 ($C_{4'}$), 146.8 (C_4), 163.3 (C_2), 167.8 (C=O), 126.5, 128.3, 128.8, 129.2, 130.5, 131.2, 133.8, 136.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{14}ClN_3OS$: C, 63.23; H, 3.71; N, 11.06; Found: C, 63.27; H, 3.69; N, 11.14%.

*5.1.2.7. 4′-Phenyl-N-(4-phenyl-1H-imidazol-2-yl)-1′H-pyrrole-3′-carboxamide (**9a**).* Brown solid (0.23 g, 73%); m.p. 206–208 °C; IR (KBr): 3270 (NH), 1681 (*C*ONH), 1573 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.58 (s, 1H, $C_{2'}$–H), 6.81 (s, 1H, $C_{5'}$–H), 7.23–7.79 (m, 11H, Ar–H and C_5–H), 8.25 (bs, 1H, CO–NH), 9.85 (bs, 1H, $C_{2'}$–NH), 11.46 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 110.1 ($C_{3'}$), 115.8 ($C_{5'}$), 121.5 (C_5), 123.8 ($C_{2'}$) 129.1 ($C_{4'}$), 137.3 (C_2), 140.1 (C_4), 168.3 (C=O), 127.4, 128.7, 129.1, 130.4, 133.5, 136.1 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06; Found: C, 73.22; H, 4.94; N, 17.17%.

*5.1.2.8. 4′-Phenyl-N-(4-p-tolyl-1H-imidazol-2-yl)-1′H-pyrrole-3′-carboxamide (**9b**).* Brown solid (0.23 g, 70%); m.p. 200–202 °C; IR (KBr): 3268 (NH), 1679 (*C*ONH), 1565 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.30 (s, 3H, Ar–CH_3), 6.54 (s, 1H, $C_{2'}$–H), 6.76 (s, 1H, $C_{5'}$–H), 7.21–7.83 (m, 10H, Ar–H and C_5–H), 8.20 (bs, 1H, CO–NH), 9.75 (bs, 1H, $C_{2'}$–NH), 11.32 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.3 (Ar–CH_3), 110.3 ($C_{3'}$), 115.1 ($C_{5'}$), 120.8 (C_5), 123.2 ($C_{2'}$), 138.5 (C_2), 139.7 (C_4), 168.0 (C=O), 128.5 ($C_{4'}$), 127.1, 127.8, 128.4, 128.9, 129.1, 130.4, 136.5, 138.2 (aromatic carbons) ppm; Anal. Calcd. for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.29; N, 16.36; Found: C, 73.61; H, 5.32; N, 16.32%.

*5.1.2.9. N-(4-(p-Chlorophenyl)-1H-imidazol-2-yl)-4′-phenyl-1′H-pyrrole-3′-carboxamide (**9c**).* Brown solid (0.27 g, 76%); m.p. 210–212 °C; IR (KBr): 3275 (NH), 1684 (*C*ONH), 1578 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.60 (s, 1H, $C_{2'}$–H), 6.84 (s, 1H, C_5′–H), 7.11–7.82 (m, 10H, Ar–H, C_5–H), 8.35 (bs, 1H, CO–NH), 9.89 (bs, 1H, $C_{2'}$–NH), 11.61 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 110.2 ($C_{3'}$), 115.7 ($C_{5'}$), 121.9 (C_5), 124.1 ($C_{2'}$) 128.9 ($C_{4'}$), 138.9 (C_2), 141.3 (C_4), 168.7 (C=O), 126.8, 127.4, 128.0, 128.9, 129.3, 131.0, 134.5, 136.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{15}ClN_4O$: C, 66.20; H, 4.16; N, 15.44; Found: C, 66.24; H, 4.18; N, 15.50%.

*5.1.3. General procedure for synthesis of 4′,5′-dihydro-4′-phenyl-N-(4-aryloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**10a**–**c**)/4′,5′-dihydro-4′-phenyl-N-(4-arylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**11a**–**c**)/4′,5′-dihydro-4′-phenyl-N-(4-aryl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**12a**–**c**)*

To a well cooled solution of **4**/**5**/**6** (2.5 mmol) in dichloromethane (10 ml) an ethereal solution of diazomethane (20 ml, 0.4 M) and triethylamine (0.1 ml) were added. The reaction mixture was kept at −20 to −15 °C for 42–48 h. The solvent was removed on a rotary evaporator. The resultant solid was purified by column chromatography (silica gel, 60–120 mesh) using hexane-ethyl acetate (4:1) as eluent.

*5.1.3.1. 4′,5′-Dihydro-4′-phenyl-N-(4-phenyloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**10a**).* Pale yellow solid (0.64 g, 78%); m.p.

199–201 °C; IR (KBr): 3281 (NH), 1674 (*C*ONH), 1624 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.60 (dd, 1H, H_X, J_{AX} = 6.1 Hz, J_{MX} = 11.1 Hz), 4.02 (dd, 1H, H_M, J_{AM} = 11.6 Hz, J_{MX} = 11.1 Hz), 4.43 (dd, 1H, H_A, J_{AM} = 11.6 Hz, J_{AX} = 6.1 Hz), 7.09–7.68 (m, 11H, Ar–H and C_5–H), 8.41 (bs, 1H, CO–NH), 8.98 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 48.3 ($C_{4'}$), 58.8 ($C_{5'}$), 139.2 (C_5), 141.3 (C_4), 142.2 ($C_{3'}$), 151.2 (C_2), 153.5 (C=O), 125.9, 126.8, 128.3, 130.3, 133.8, 139.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.85; Found: C, 68.72; H, 4.84; N, 16.89%.

*5.1.3.2. 4′,5′-Dihydro-4′-phenyl-N-(4-p-tolyloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**10b**).* Pale yellow solid (0.64 g, 75%); m.p. 216–218 °C; IR (KBr): 3275 (NH), 1671 (*C*ONH), 1619 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3H, Ar–CH_3), 3.58 (dd, 1H, H_X, J_{AX} = 6.0 Hz, J_{MX} = 11.0 Hz), 4.00 (dd, 1H, H_M, J_{AM} = 11.5 Hz, J_{MX} = 11.0 Hz), 4.39 (dd, 1H, H_A, J_{AM} = 11.5 Hz, J_{AX} = 6.0 Hz), 7.06–7.70 (m, 10H, Ar–H and C_5–H), 8.38 (bs, 1H, CO–NH), 8.92 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.2 (Ar–CH_3), 48.1 ($C_{4'}$), 58.5 ($C_{5'}$), 139.0 (C_5), 140.8 (C_4), 142.0 ($C_{3'}$), 150.0 (C_2), 153.2 (C=O), 125.7, 126.3, 127.8, 128.5, 130.1, 130.8, 138.3, 139.7 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.34; H, 5.23; N, 16.17; Found: C, 69.38; H, 5.26; N, 16.11%.

*5.1.3.3. N-(4-(p-Chlorophenyl)oxazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**10c**).* Pale yellow solid (0.74 g, 81%); m.p. 224–226 °C; IR (KBr): 3288 (NH), 1677 (*C*ONH), 1628 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.62 (dd, 1H, H_X, J_{AX} = 6.2 Hz, J_{MX} = 11.2 Hz), 4.08 (dd, 1H, H_M, J_{AM} = 11.7 Hz, J_{MX} = 11.2 Hz), 4.47 (dd, 1H, H_A, J_{AM} = 11.7 Hz, J_{AX} = 6.2 Hz), 7.07–7.71 (m, 10H, Ar–H and C_5–H), 8.42 (bs, 1H, CO–NH), 9.00 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 48.5 ($C_{4'}$), 58.9 ($C_{5'}$), 139.5 (C_5), 141.4 (C_4), 142.7 ($C_{3'}$), 150.5 (C_2), 153.9 (C=O), 126.0, 127.4, 127.8, 128.5, 129.3, 130.0, 137.5, 139.9 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{15}ClN_4O_2$: C, 62.21; H, 4.12; N, 15.27; Found: C, 62.17; H, 4.14; N, 15.32%.

*5.1.3.4. 4′,5′-Dihydro-4′-phenyl-N-(4-phenylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**11a**).* Pale yellow solid (0.61 g, 71%); m.p. 213–215 °C; IR (KBr): 3319 (NH), 1653 (*C*ONH), 1592 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.58 (dd, 1H, H_X, J_{AX} = 6.1 Hz, J_{MX} = 11.3 Hz), 4.21 (dd, 1H, H_M, J_{AM} = 11.9 Hz, J_{MX} = 11.3 Hz), 4.38 (dd, 1H, H_A, J_{AM} = 11.9 Hz, J_{AX} = 6.1 Hz), 7.17–7.74 (m, 11H, Ar–H and C_5–H), 8.48 (bs, 1H, CO–NH), 8.81 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 47.8 ($C_{4'}$), 56.3 ($C_{5'}$), 103.6 (C_5), 141.5 ($C_{3'}$), 149.8 (C_4), 164.2 (C_2), 167.4 (C=O), 126.5, 127.6, 128.9, 129.8, 133.2, 139.0 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{16}N_4OS$: C, 65.49; H, 4.62; N, 16.08; Found: C, 65.56; H, 4.60; N, 16.16%.

*5.1.3.5. 4′,5′-Dihydro-4′-phenyl-N-(4-p-tolylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**11b**).* Pale yellow solid (0.71 g, 79%); m.p. 230–232 °C; IR (KBr): 3310 (NH), 1650 (*C*ONH), 1580 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 3H, Ar–CH_3), 3.54 (dd, 1H, H_X, J_{AX} = 6.1 Hz, J_{MX} = 11.1 Hz), 4.18 (dd, 1H, H_M, J_{AM} = 11.6 Hz, J_{MX} = 11.1 Hz), 4.34 (dd, 1H, H_A, J_{AM} = 11.6 Hz, J_{AX} = 6.1 Hz), 7.19–7.81 (m, 10H, Ar–H and C_5–H), 8.46 (bs, 1H, CO–NH), 8.80 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.5 (Ar–CH_3), 47.2 ($C_{4'}$), 56.0 ($C_{5'}$), 102.0 (C_5), 141.0 ($C_{3'}$), 149.1 (C_4), 163.9 (C_2), 166.3 (C=O), 125.8, 127.0, 128.2, 128.8, 129.7, 130.9, 137.7, 139.4 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{18}N_4OS$: C, 66.27; H, 5.00; N, 15.45; Found: C, 66.32; H, 5.03; N, 15.50%.

*5.1.3.6. N-(4-(p-Chlorophenyl)thiazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**11c**).* Pale yellow solid (0.76 g, 80%); m.p. 237–239 °C; IR (KBr): 3340 (NH), 1662 (*C*ONH), 1601 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.59 (dd, 1H, H_X, J_{AX} = 6.0 Hz, J_{MX} = 11.3 Hz), 4.23 (dd, 1H, H_M, J_{AM} = 11.5 Hz, J_{MX} = 11.3 Hz), 4.41 (dd, 1H, H_A, J_{AM} = 11.5 Hz, J_{AX} = 6.0 Hz), 7.08–7.73 (m, 10H, Ar–H and C_5–H), 8.51 (bs, 1H, CO–NH), 8.83 (bs, 1H, N–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 48.2 ($C_{4'}$), 56.8 ($C_{5'}$), 104.2 (C_5), 142.3 ($C_{3'}$), 150.2 (C_4), 164.8 (C_2), 167.5 (C=O), 127.7, 128.5, 128.7, 129.1, 129.6, 131.5, 135.0, 136.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{15}ClN_4OS$: C, 59.60; H, 3.94; N, 14.63; Found: C, 59.67; H, 3.92; N, 14.60%.

*5.1.3.7. 4′,5′-Dihydro-4′-phenyl-N-(4-phenyl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**12a**).* Pale yellow solid (0.63 g, 77%); m.p. 222–224 °C; IR (KBr): 3243 (NH), 1684 (*C*ONH), 1594 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.66 (dd, 1H, H_X, J_{AX} = 6.4 Hz, J_{MX} = 11.3 Hz), 4.11 (dd, 1H, H_M, J_{AM} = 11.5 Hz, J_{MX} = 11.3 Hz), 4.40 (dd, 1H, H_A, J_{AM} = 11.5 Hz, J_{AX} = 6.4 Hz), 7.19–7.70 (m, 11H, Ar–H and C_5–H), 8.02 (bs, 1H, CO–NH), 8.13 (bs, 1H, N–NH), 11.21 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 48.6 ($C_{4'}$), 59.1 ($C_{5'}$), 119.7 (C_5), 134.2 (C_2), 141.0 (C_4), 143.2 ($C_{3'}$), 153.5 (C=O), 127.5, 128.3, 129.5, 130.0, 133.0, 136.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{17}N_5O$: C, 68.86; H, 5.16; N, 21.13; Found: C, 68.81; H, 5.18; N, 21.24%.

*5.1.3.8. 4′,5′-Dihydro-4′-phenyl-N-(4-p-tolyl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**12b**).* Pale yellow solid (0.64 g, 75%); m.p. 241–243 °C; IR (KBr): 3237 (NH), 1681 (*C*ONH), 1582 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3H, Ar–CH_3), 3.64 (dd, 1H, H_X, J_{AX} = 6.7 Hz, J_{MX} = 11.4 Hz), 4.09 (dd, 1H, H_M, J_{AM} = 11.4 Hz, J_{MX} = 11.4 Hz), 4.41 (dd, 1H, H_A, J_{AM} = 11.4 Hz, J_{AX} = 6.7 Hz), 7.06–7.65 (m, 10H, Ar–H and C_5–H), 8.00 (bs, 1H, CO–NH), 8.11 (bs, 1H, N–NH), 11.19 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.0 (Ar–CH_3), 47.3 ($C_{4'}$), 58.2 ($C_{5'}$), 119.1 (C_5), 133.1 (C_2), 140.5 (C_4), 143.0 ($C_{3'}$), 153.2 (C=O), 127.2, 127.5, 128.2, 128.9, 129.6, 135.8, 138.1 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{19}N_5O$: C, 69.54; H, 5.54; N, 20.27; Found: C, 69.60; H, 5.51; N, 20.36%.

*5.1.3.9. N-(4-(p-Chlorophenyl)-1H-imidazol-2-yl)-4′,5′-dihydro-4′-phenyl-1′H-pyrazole-3′-carboxamide (**12c**).* Pale yellow solid (0.66 g, 73%); m.p. 250–252 °C; IR (KBr): 3245 (NH), 1688 (*C*ONH), 1605 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 3.68 (dd, 1H, H_X, J_{AX} = 6.3 Hz, J_{MX} = 11.2 Hz), 4.16 (dd, 1H, H_M, J_{AM} = 11.6 Hz, J_{MX} = 11.2 Hz), 4.47 (dd, 1H, H_A, J_{AM} = 11.6 Hz, J_{AX} = 6.3 Hz), 7.20–7.74 (m, 10H, Ar–H and C_5–H), 8.08 (bs, 1H, NH), 8.25 (bs, 1H, N–NH), 11.71 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 48.9 ($C_{4'}$), 59.1 ($C_{5'}$), 119.9 (C_5), 134.6 (C_2), 141.5 (C_4), 143.6 ($C_{3'}$), 153.9 (C=O), 126.8, 127.3, 128.1, 129.4, 129.8, 131.3, 134.4, 136.2 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.40; N, 19.14; Found: C, 62.32; H, 4.43; N, 19.20%.

*5.1.4. General procedure for synthesis of 4′-phenyl-N-(4-aryloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**13a–c**)/4′-phenyl-N-(4-arylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**14a–c**)/4′-phenyl-N-(4-aryl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**15a–c**)*

The compound **10**/**11**/**12** (1 mmol), chloranil (0.29 g, 1.2 mmol) and xylene (10 ml) were refluxed for 24–25 h. Then, it was treated with 5% NaOH solution. The organic layer was separated and repeatedly washed with water and dried. The solvent was removed *in vacuo*. The solid obtained was purified by recrystallization from 2-propanol.

*5.1.4.1. 4′-Phenyl-N-(4-phenyloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**13a**).* White solid (0.21 g, 64%); m.p. 228–230 °C; IR (KBr): 3242 (NH), 1643 (*C*ONH), 1627 (C=C), 1578 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.24 (s, 1H, $C_{5'}$–H), 6.61 (bs, 1H, N–NH), 6.82–7.63 (m, 11H, Ar–H and C_5–H), 8.52 (bs, 1H, CO–NH) ppm; ^{13}C

NMR (DMSO-d_6, 100 MHz): δ 123.9 ($C_{4'}$), 130.3 ($C_{3'}$), 131.5 ($C_{5'}$), 138.6 (C_5), 140.3 (C_4), 148.4 (C_2), 164.1 (C=O), 127.4, 128.3, 129.4, 130.5, 133.1, 136.5 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96; Found: C, 69.16; H, 4.29; N, 16.90%.

*5.1.4.2. 4′-phenyl-N-(4-p-tolyloxazol-2-yl)-1′H-pyrazole-3′-carboxamide (**13b**).* White solid (0.22 g, 66%); m.p. 240–242 °C; IR (KBr): 3236 (NH), 1638 (*C*ONH), 1633 (C=C), 1565 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 3H, Ar–CH_3), 6.21 (s, 1H, $C_{5'}$–H), 6.58 (bs, 1H, N–NH), 6.74–7.54 (m, 10H, Ar–H and C_5–H), 8.47 (bs, 1H, CO–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 23.5 (Ar–CH_3), 123.2 ($C_{4'}$), 130.0 ($C_{3'}$), 131.1 ($C_{5'}$), 138.3 (C_5), 140.1 (C_4), 147.1 (C_2), 163.8 (C=O), 125.4, 125.0, 127.3, 129.0, 131.1, 133.6, 136.1 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.75; H, 4.68; N, 16.26; Found: C, 69.80; H, 4.65; N, 16.30%.

*5.1.4.3. N-(4-(p-Chlorophenyl)oxazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**13c**).* White solid (0.25 g, 69%); m.p. 254–256 °C; IR (KBr): 3250 (NH), 1645 (*C*ONH), 1630 (C=C), 1581 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.26 (s, 1H, $C_{5'}$–H), 6.65 (bs, 1H, N–NH), 6.91–7.68 (m, 10H, Ar–H and C_5–H), 8.58 (bs, 1H, CO–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 124.2 ($C_{4'}$), 130.7 ($C_{3'}$), 131.6 ($C_{5'}$), 138.0 (C_5), 139.7 (C_4), 147.8 (C_2), 164.7 (C=O), 125.5, 126.2, 127.7, 129.2, 131.2, 132.1, 133.4, 136.4 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{13}ClN_4O_2$: C, 62.55; H, 3.59; N, 15.35; Found: C, 62.63; H, 3.60; N, 15.43%.

*5.1.4.4. 4′-Phenyl-N-(4-phenylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**14a**).* White solid (0.23 g, 67%); m.p. 232–234 °C; IR (KBr): 3328 (NH), 1652 (*C*ONH), 1634 (C=C), 1583 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.31 (s, 1H, $C_{5'}$–H), 6.40 (bs, 1H, N–NH), 6.68–7.32 (m, 11H, Ar–H and C_5–H), 8.81 (bs, 1H, CO–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 104.6 (C_5), 125.3 ($C_{4'}$), 130.7 ($C_{3'}$), 133.1 ($C_{5'}$), 147.0 (C_4), 162.4 (C_2), 164.8 (C=O), 126.2, 127.4, 130.4, 131.6, 133.1, 136.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{14}N_4OS$: C, 65.87; H, 4.07; N, 16.17; Found: C, 65.80; H, 4.04; N, 16.23%.

*5.1.4.5. 4′-Phenyl-N-(4-p-tolylthiazol-2-yl)-1′H-pyrazole-3′-carboxamide (**14b**).* White solid (0.25 g, 70%); m.p. 257–259 °C; IR (KBr): 3323 (NH), 1660 (*C*ONH), 1628 (C=C), 1579 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.31 (s, 3H, Ar–CH_3), 6.28 (s, 1H, $C_{5'}$–H), 6.38 (bs, 1H, N–NH), 6.58–7.24 (m, 10H, Ar–H and C_5–H), 8.77 (bs, 1H, CO–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 24.0 (Ar–CH_3), 103.1 (C_5), 124.7 ($C_{4'}$), 130.0 ($C_{3'}$), 132.4 ($C_{5'}$) 146.5 (C_4), 161.1 (C_2), 164.2 (C=O), 125.4, 126.2, 127.6, 129.8, 130.4, 131.6, 132.7, 133.4, 136.3 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{16}N_4OS$: C, 66.64; H, 4.47; N, 15.54; Found: C, 66.71; H, 4.49; N, 15.58%.

*5.1.4.6. N-(4-(p-Chlorophenyl)thiazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**14c**).* White solid (0.27 g, 72%); m.p. 263–265 °C; IR (KBr): 3343 (NH), 1672 (*C*ONH), 1637 (C=C), 1598 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.41 (s, 1H, $C_{5'}$–H), 6.27 (bs, 1H, N–NH), 6.51–7.12 (m, 10H, Ar–H and C_5–H), 8.88 (bs, 1H, CO–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 103.8 (C_5), 125.2 ($C_{4'}$), 131.5 ($C_{3'}$), 133.9 ($C_{5'}$) 147.8 (C_4), 161.8 (C_2), 164.9 (C=O), 125.6, 126.3, 128.4, 129.1, 131.6, 132.4, 133.0, 136.4 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{13}ClN_4OS$: C, 59.91; H, 3.43; N, 14.71; Found: C, 59.07; H, 3.40; N, 14.78%.

*5.1.4.7. 4′-Phenyl-N-(4-phenyl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**15a**).* White solid (0.20 g, 63%); m.p. 240–242 °C; IR (KBr): 3248 (NH), 1656 (*C*ONH), 1641 (C=C), 1576 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.12 (s, 1H, $C_{5'}$–H), 6.52 (bs, 1H, N–NH), 6.82–7.61 (m, 11H, Ar–H and C_5–H), 8.83 (bs, 1H, CO–NH), 11.00 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 120.6 (C_5), 126.4 ($C_{4'}$), 132.8 ($C_{3'}$), 134.2 ($C_{5'}$), 138.4 (C_2), 140.3 (C_4), 164.1 (C=O), 124.3, 127.3, 130.1, 132.1, 133.4, 136.6 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{15}N_5O$: C, 69.28; H, 4.59; N, 21.26; Found: C, 69.36; H, 4.61; N, 21.30%.

*5.1.4.8. 4′-Phenyl-N-(4-p-tolyl-1H-imidazol-2-yl)-1′H-pyrazole-3′-carboxamide (**15b**).* White solid (0.22 g, 65%); m.p. 272–274 °C; IR (KBr): 3235 (NH), 1668 (*C*ONH), 1645 (C=C), 1563 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.41 (s, 3H, Ar–CH_3) 6.08 (s, 1H, $C_{5'}$–H), 6.50 (bs, 1H, N–NH), 6.80–7.60 (m, 10H, Ar–H and C_5–H), 8.80 (bs, 1H, CO–NH), 10.98 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 23.5 (Ar–CH_3), 120.3 (C_5), 125.1 ($C_{4'}$), 132.4 ($C_{3'}$), 133.6 ($C_{5'}$), 138.0 (C_2), 139.8 (C_4), 163.0 (C=O), 125.4, 126.6, 127.0, 129.0, 131.3, 132.1, 133.2, 136.4 (aromatic carbons) ppm; Anal. Calcd. for $C_{20}H_{17}N_5O$: C, 69.95; H, 4.98; N, 20.39; Found: C, 69.91; H, 4.97; N, 20.48%.

*5.1.4.9. N-(4-(p-Chlorophenyl)-1H-imidazol-2-yl)-4′-phenyl-1′H-pyrazole-3′-carboxamide (**15c**).* White solid (0.24 g, 68%); m.p. 280–282 °C; IR (KBr): 3251 (NH), 1673 (*C*ONH), 1638 (C=C), 1580 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 6.34 (s, 1H, $C_{5'}$–H), 6.61 (bs, 1H, N–NH), 6.78–7.64 (m, 10H, Ar–H and C_5–H), 8.89 (bs, 1H, CO–NH), 11.41 (bs, 1H, C_5–NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 121.0 (C_5), 126.7 ($C_{4'}$), 133.4 ($C_{3'}$), 135.6 ($C_{5'}$), 139.3 (C_2), 140.7 (C_4), 164.5 (C=O), 125.3, 126.8, 127.5, 128.3, 131.6, 132.4, 133.6, 136.0 (aromatic carbons) ppm; Anal. Calcd. for $C_{19}H_{14}ClN_5O$: C, 62.72; H, 3.87; N, 19.24; Found: C, 62.78; H, 3.90; N, 19.35%.

5.2. Biological assays

5.2.1. Compounds

The compounds **4**–**15** were dissolved in DMSO at different concentrations of 50 and 100 μg/mL.

5.2.2. Cells

Bacterial strains *Staphylococcus aureus*, *B. subtilis*, *P. aeruginosa*, *Klebsiella pneumoniae* and fungi *A. niger* and *P. chrysogenum* were obtained from Department of Microbiology, S.V University, Tirupati, India.

5.2.3. Antibacterial and antifungal assays

The *in-vitro* antimicrobial studies were carried out by agar well diffusion method against test organisms [31,32]. Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 μl) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petriplate. The compounds were dissolved in DMSO of 5 mg/ml and from this 10 μl and 20 μl (50, 100 μg/well) were added into the wells by using sterile pipettes. Simultaneously the standard antibiotics, Chloramphenicol for antibacterial activity and Ketoconazole for antifungal activity (as positive control) were tested against the pathogens. The samples were dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antibacterial activity.

Broth dilution test is used to determine Minimum Inhibitory Concentration (MIC) of the above mentioned samples [33,34]. Freshly prepared nutrient broth was used as diluents. The 24 h old culture of the test bacteria *S. aureus*, *B. subtilis*, *P. aeruginosa and K. pneumoniae* and the test fungi *A. niger* and *P. chrysogenum* were diluted 100 folds in nutrient broth (100 μl bacterial cultures in

10 ml NB). The stock solution of the synthesized compounds was prepared in dimethyl sulfoxide (DMSO) by dissolving 5 mg of the compound in 1 ml of DMSO. Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 μl of stock solution contains 6.25, 12.5, 25, 50, 100, 200 μg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. Control without test samples and with solvent was assayed simultaneously. The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC.

To determine the Minimum Bactericidal Concentration (MBC) [35] and Minimum Fungicidal Concentration (MFC) [36] for each set of test tubes in the MIC determination, a loopful of broth was collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi were incubated at 37 °C for 24 h and at 28 °C for 48 h, respectively. After incubation, the lowest concentration was noted as MBC (for bacteria) or MFC (for fungi) at which no visible growth was observed.

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